Contains Nonbinding Recommendations

Draft Guidance on Azelaic Acid

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Azelaic Acid

Form/Route: Gel/Topical

Recommended studies: 1 study

Type of study: Clinical Endpoint Bioequivalence (BE) Study
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 15%
Subjects: Healthy males and females with rosacea.
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional comments regarding the clinical endpoint BE study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study in the treatment of moderate rosacea. Subjects are to be randomized to receive the generic Azelaic Acid topical gel, 15%, the reference listed drug (RLD), or placebo twice daily for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (study Week 12).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Healthy male or nonpregnant female aged ≥ 18 years with a clinical diagnosis of moderate facial rosacea, defined as the presence of:
      i. At least eight and not more than fifty inflammatory facial lesions (i.e., papules/pustules), AND
      ii. Persistent erythema, AND
      iii. Telangiectasia.
   b. Subject willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages).

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period.
   b. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.

c. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
d. History of hypersensitivity or allergy to propylene glycol or any other component of the formulation.
e. Use within 6 months prior to baseline of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
f. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
g. Use within 1 month prior to baseline of 1) topical retinoids to the face, 2) systemic antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim), or 3) systemic corticosteroids.
h. Use within 2 weeks prior to baseline of 1) topical corticosteroids, 2) topical antibiotics or 3) topical medications for rosacea (e.g., metronidazole, azelaic acid).
i. Subjects with moderate or severe rhinophyma, dense telangiectases, or plaque-like facial edema.
j. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
   a. Any other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids).
   b. Oral retinoids.
   c. Systemic (e.g., oral or injectable) antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives).
   d. Systemic corticosteroid or immunosuppressive drugs.
   e. Antipruritics, including antihistamines, within 24 hours of study visits.

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Occlusive dressings or wrappings should be avoided in treatment areas. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

6. Areas to be treated should be washed with a mild cleanser before application and patted dry with a soft towel. A thin layer of study treatment should be gently massaged into the affected areas on the face twice daily, in the morning and evening, for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands should be washed following application.

7. The recommended primary endpoint of the study is the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts. The protocol should clearly define papules, pustules, and nodules. When counting facial lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules should be reported separately and not included in the inflammatory lesion counts.

8. An Investigator's Global Evaluation (IGE) should be evaluated as a secondary endpoint for the statistical analysis. The IGE should be a static scale, describing the extent of disease associated with each score. This scale should not be a reflection of treatment response, but should describe the condition at each visit. Therefore, no reference should be made to baseline in the evaluation.

The scale should be dichotomized into "success" and "failure". "Success" should be defined either as a score consistent with clear or almost clear at the final visit.

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules

9. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.

10. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) OR discontinued from the study as a treatment failure, and did not have any protocol violations. The PP population should be used for the bioequivalence evaluation of test vs. reference. The protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study treatment doses) and specify how compliance will be verified (e.g., by the use of subject diaries).

11. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.

12. The safety population includes all randomized subjects who received study treatment.

13. Subjects who discontinued early from the study due to lack of treatment effect after completing at least eight weeks of treatment should be included in the mITT and PP population as treatment failures and the change in inflammatory lesion count from the baseline visit to the last completed visit prior to discontinuation due to lack of efficacy should be carried forward in the primary endpoint analysis. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

14. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

15. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.

16. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved

in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

17. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

18. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

19. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

20. To establish bioequivalence for the primary endpoint, the 90% confidence interval for the test/reference ratio of mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts must be contained within [0.80, 1.25] for a continuous variable, using the PP population. To establish bioequivalence for the secondary endpoint, the 90% confidence interval for the test/reference ratio of success rate on the Investigator's Global Evaluation (IGE) should be contained within [-0.20, +0.20] for a dichotomous variable, using the PP population.

21. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint (mean percent change from baseline), using the mITT study population and LOCF.

22. The following Statistical Analysis Method is recommended for equivalence testing for a continuous variable:

    <u>Equivalence Analysis for a Continuous Variable</u>

    The compound hypothesis to be tested is:

    H_0: $\mu_T / \mu_R \leq \theta_1$ or $\mu_T / \mu_R \geq \theta_2$ versus H_A: $\theta_1 < \mu_T / \mu_R < \theta_2$

    Where μ_T = mean of test treatment, and μ_R = mean of reference treatment

    Typically, we reject H_0 with a type I error $\alpha = 0.05$ (two 1-sided tests), if the 90% confidence interval for the ratio of means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$.

    Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

23. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

    Equivalence Analysis for a Dichotomous Variable

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

    H_A: $-0.20 \leq p_T - p_R \leq 0.20$

    where p_T = cure rate of test treatment and p_R = cure rate of reference treatment.

    Let
    n_T = sample size of test treatment group
    cn_T = number of cured subjects in test treatment group
    n_R = sample size of reference treatment group
    cn_R = number of cured subjects in reference treatment group

    $\hat{p}_T = \text{c}n_T / n_T$, $\hat{p}_R = \text{c}n_R / n_R$,

    and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

    The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

    $L = (\hat{p}_T - \hat{p}_R) - 1.645\ \text{se} - (1/n_T + 1/n_R)/2$

    $U = (\hat{p}_T - \hat{p}_R) + 1.645\ \text{se} + (1/n_T + 1/n_R)/2$

    We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

    Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

24. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included.

b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
e. Please provide a separate dataset for variables such as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

25. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of Actual Treatment (exposure): test product, RLD, placebo
    i. Duration of Treatment (total exposure in days)
    j. Per Protocol (PP) population inclusion (yes/no)
    k. Reason for exclusion from PP population
    l. Modified Intent to Treat (mITT) population inclusion (yes/no)
    m. Reason for exclusion from mITT population
    n. Safety population inclusion (yes/no)
    o. Reason for exclusion from safety population
    p. Baseline lesion count (papules and pustules)
    q. Week 12 lesion count (papules and pustules)
    r. Treatment compliance: number of missed doses per subject
    s. Concomitant medication (yes/no)
    t. Adverse event(s) reported (yes/no)

    Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	lesion-b	lesion12	complian	CM	AE
101	1	01	22	YEARS	F	1	A	28	Y		Y		Y		8	2	0	Y	Y
101	2	01	30	YEARS	F	1	B	28	Y		Y		Y		7	1	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo
EXDUR:	Duration of Treatment (total exposure in days)
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, B=negative baseline culture, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
lesion_b:	Baseline lesion count (total number of papules and pustules at baseline)
lesion12:	Week 12 lesion count (total number of papules and pustules at Week 12)
complian:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

26. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Evaluator: identity of evaluator
    h. Papule count
    i. Pustule count
    j. Nodule count
    k. Erythema score
    l. IGE score
    m. Concomitant medication reported during this visit (yes/no)
    n. Adverse event reported during this visit (yes/no)
    o. Laboratory testing during this visit (yes/no)

    Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	papule	pustule	nodule	eryth	ige	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0	JB	4	4	0	2	3	Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
EVAL:	Evaluator: identity of the evaluator, e.g., initials
papule:	number of papules
pustule:	number of pustules
nodule:	number of nodules
eryth:	Erythema score, e.g. 0=none, 1=Mild, 2=Moderate, 3=Severe
ige:	IGE score, e.g., 0=Clear, 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

27. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of azelaic acid.